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A New Concept for the Preparation of β-L- and β-D-2′,3′-Dideoxynucleoside Analogues

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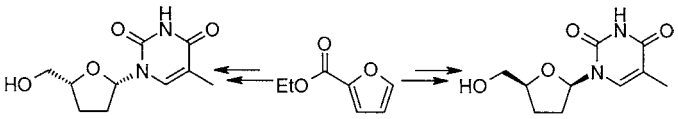
ABSTRACT



A new method for the synthesis of 2′,3′-dideoxynucleoside analogues has been developed. An electrochemical activation of 2-substituted furans is followed by the coupling with a pyrimidine or purine base. This gives planar furyl nucleosides as key intermediates, which are hydrogenated *cis*-selectively to give the corresponding β-2′,3′-dideoxynucleosides as racemic mixtures. An enzymatic kinetic resolution gives rise to β-D- and β-L-configured derivatives in high optical purity. This is exemplified by the synthesis of β-D- and β-L-3′-deoxythymidine.

Since the first synthesis of a pyrimidine 2′,3′-dideoxynucleoside, 3′-deoxythymidine, described by Michelson and Todd in 1955,[1] a huge number of 2′,3′-dideoxynucleoside analogues (ddNs) has been prepared. The reason for interest in this family of compounds is based on the finding that ddNs are potentially effective therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS) and other virus-caused diseases.[2] Four of the six nucleoside analogues that are approved anti-HIV drugs, namely, Zidovudine (AZT),[3] Didanosine (ddI),[4] Zalcitabine (ddC),[5] and Stavudine (d4T),[6a] re derivatives of the naturally occurring nucleosides. These compounds all have one thing in common, namely, a β-D-configuration in their sugar moieties. All of these drugs and other nucleoside analogues are believed to have a similar mechanism of HIV inhibition, in which the analogues are progressively phosphorylated by cytoplasmic enzymes to nucleoside 5′-triphosphates. These then compete with the natural nucleoside triphosphate substrate for binding to cellular DNA polymerase and the viral reverse transcriptase.

More recently, a number of nucleoside analogues, possessing the unnatural β-L-configuration, have emerged as potential antiviral agents. Research was encouraged by the fact that L-nucleosides are generally endowed with lower host toxicity while maintaining good antiviral/antibacterial activity.[7] Lamivudine (3TC) is the first compound out of that family that has been approved for use in combination therapy against HIV and HBV.[8] Other promising candidates with notedly good antiviral profiles are β-L-ddC,[9] β-L-Fd4C,[10] or β-L-FddC[11] (Figure 1).

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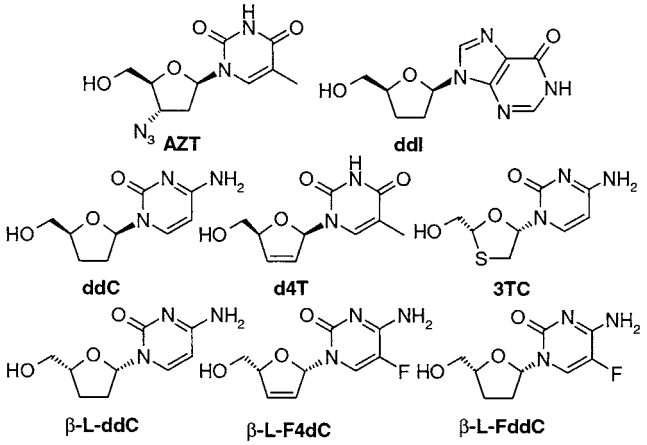


Figure 1. Structures of relevant nucleoside analogues.

A common structural feature of all active nucleoside analogues is determined through the *cis*-arrangement of the hydroxymethyl side chain to the nucleobase (*β*-configuration). Syntheses for D-configured nucleoside analogues, starting from naturally occurring nucleosides, are well elaborated. The hydroxy groups at C-2′ and C-3′ can be removed by a number of reactions without affecting the glycosyl bond. Rather expensive starting materials and a limited range of accessible products narrow this approach.[12]

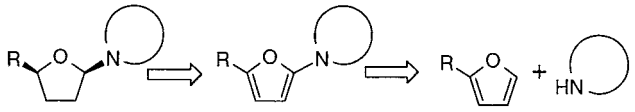
Alternatively, the fusion of a suitable sugar part or a carba- or heterocyclic equivalent with an activated base can give rise to the corresponding D- and L-configurated nucleoside analogues and other unnatural nucleoside derivatives. Thereby, problems concerning the α/*β* selectivity of the coupling reaction are usually encountered. This can be overcome by the introduction of an anchimerically assisting group at position 2 or 3 of the sugar moiety that has to be removed at the end of the synthesis, thus rendering the sequence laborious.[13]

A de novo approach to D- and L-nucleosides starting from furan was described by Trost and Shi.[14] Palladium-catalyzed desymmetrization of a *cis*-2,5-diacyloxy-2,5-dihydrofuran (prepared by reaction of lead tetraacyloxylates with furan) enables the subsequent introduction of the nucleobase and the side chain, thereby allowing access to both enantiomeric series.

However, all the existing methods for the synthesis of 2′,3′-dideoxynucleosides suffer from at least one of these drawbacks: expensive starting materials, toxic reagents, lack of control during the glycosylation, and lengthy synthesis.

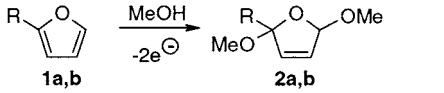
Bearing that in mind, we anticipated that furoic acid, furfural, or furyl methanol derivatives, which are available in large scale, represent ideal starting materials for such a synthesis, since they already consist of the five-carbon skeleton of the final product. The coupling of a suitable furan derivative with a heterocycle should yield prochiral planar furyl nucleosides as key intermediates. The high reactivity of the furan moiety should allow a chemoselective reduction in the presence of an unsaturated *N*-heterocycle. By choosing a proper catalyst the hydrogenation should proceed in a highly *cis*-selective manner, thus fixing the desired *β*-configuration and yielding 2′,3′-dideoxynucleosides as a racemic mixture (Scheme 1).

Scheme 1. Retrosynthetic Analysis



Since there was no general method for the synthesis of furyl nucleosides starting from non-nucleoside-derived precursors,[15] we were looking for a convenient route to obtain this class of compounds. Initial attempts to couple 2-bromo-5-substituted furans or 5-substituted furyl-2-boronic acids or esters, respectively, with pyrimidine or purine derivatives, employing palladium[16] or copper[17] catalysis, either failed or gave unsatisfying results. Because of the obvious restriction of the catalyzed (and uncatalyzed) nucleophilic aromatic substitution at position 2 of furans, we decided to use well elaborated acetal chemistry for the coupling reaction. In 1952 Clauson-Kaas described the electrochemical oxidative dimethoxylation of some 2-substituted furans.[18] The reaction tolerates both furoic acid (**1a**) and furyl methanol derivatives (**1b**) and can easily be performed in a 100 g scale to give 2-substituted-2,5-dimethoxy-2,5-dihydrofurans (**2a** and **b**) in very good yields (Scheme 2).

Scheme 2. Electrochemical Activation of Furans According to Clauson-Kaas



1a,b **2a,b**

1a R = CO_2Et **2a** R = CO_2Me (70%)

1b R = CH_2OPiv **2b** R = CH_2OPiv (91%)

To our delight, it turned out that compound **2a** can easily be coupled with TMS-thymine in the presence of TMSOTf to give **3a** as a mixture of diastereoisomers in 90% yield.[19]

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By treatment of **3a** with TMSOTf (1 equiv) in acetonitrile, elimination together with rearomatization occurred consequently. Thereby, *one* single product was obtained from *four* stereoisomers (94% yield). Since these furyl nucleosides can exist as a pair of atropisomers (see Figure 2), we started

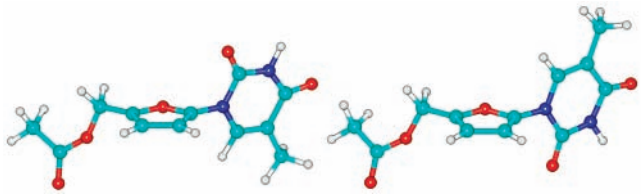


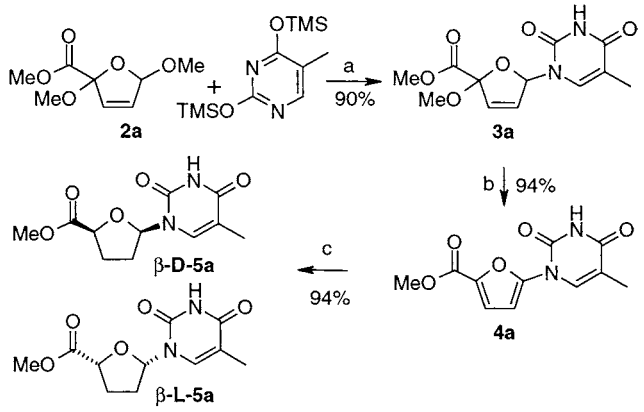
Figure 2. Hyperchem calculations indicate a rotational barrier of 8 kJ/mol.

some dynamic ^{1}H NMR experiments with **4b** (for synthesis, see Scheme 5) with and without chiral additives.[20]

In contrast to results obtained by Akhrem et al.,[15c] who claimed to have isolated optically active furyl nucleosides at room temperature (from cyclic nucleoside derived precursors), no direct observation of atropisomers, even at −100 °C, could be observed in our case. Additional molecular modeling calculations suggest a rotational barrier of 8 kJ/mol, which corroborates our results.

Compound **4a** could finally be hydrogenated *cis*-selectively to the corresponding *β*-D- and *β*-L-dideoxynucleoside derivatives (**5a**) with Rh/Al_2O_3 in methanol in 94% yield (Scheme 3). The double bond of the pyrimidine ring remained unaffected.

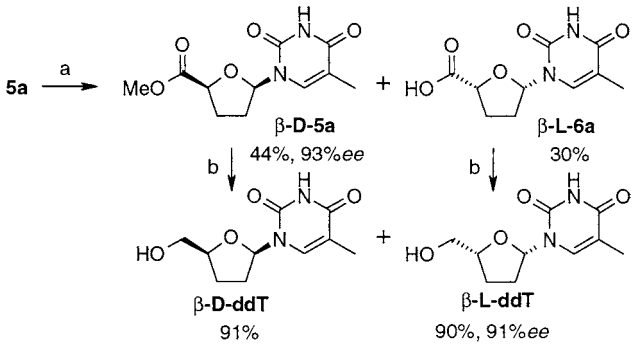
Scheme 3. Coupling, Elimination, and Hydrogenation[a]



[a] Reagents and conditions: (a) TMSOTf, CH_3CN, −30 °C to rt; (b) TMSOTf, CH_3CN, rt; (c) H_2 (1 bar), Rh/Al_2O_3 (5%), MeOH.

An enzymatic screening with a series of commercially available enzymes using racemic **5a** as substrates revealed that pig liver esterase selectively hydrolyzed *β*-L-**5a**, thus allowing the separation of the two enantiomers. The reduction with $NaBH_4$ completed the synthesis of *β*-D-ddT and *β*-L-ddT in good (unoptimized) yields and high optical purity.

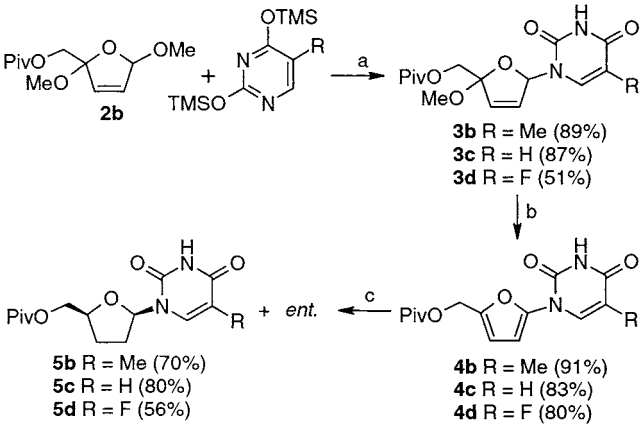
Scheme 4. Kinetic Enzymatic Resolution of Racemic **5a**[a]



[a] Reagents and conditions: (a) pig liver esterase, pH 7.4, 0.1 M NaH_2PO_4 buffer; (b) $NaBH_4$, H_2O.

The extension of this principle to 2,5-dimethoxy-2,5-dihydrofuran **2b** as starting material and other pyrimidine derivatives (in addition to thymine) was subsequently investigated. As outlined in Scheme 5, the tandem reaction

Scheme 5[a]



[a] Reagents and conditions: (a) 0.2 equiv of TMSOTf, CH_3CN, −30 °C to rt; (b) TMSBr, CH_3CN, rt; (c) see text.

consisting of coupling and elimination (with TMSBr as catalyst) leads, via **3b**−**d**, to the desired furyl nucleosides

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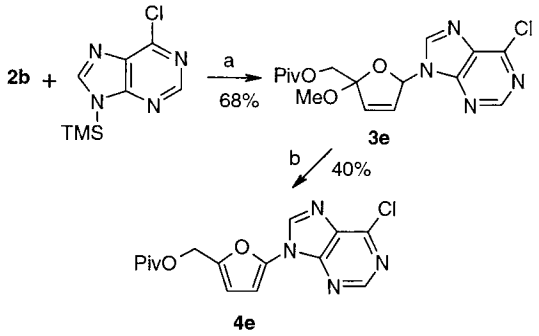
Scheme 6[a]



[a] Reagents and conditions: (a) 0.2 equiv of TMSOTf, CH_3CN, −30 °C to rt; (b) 1 equiv of BCl_3, CH_3CN, rt.

4b−**d** in good to excellent yields. The hydrogenation of **4b** and **4d** was successful when Pd/C in *MeOH* was used as catalyst. However, this system led to the reduction of both the furan and the pyrimidine in the case of the uracil-derivative **4c**. This problem has been overcome by using less reactive Pd/C in *EtOAc*, yielding racemic **5c** in good yield (80%). Some hydrogenolytic cleavage of the C−N bond was observed as a side reaction in each case. An enzyme-catalyzed hydrolysis of acyl-protected or an enzyme-catalyzed acyl transfer to unprotected analogues of **5b**−**d** should enable access to the corresponding enantiomerically pure β-L- and β-D-derivatives.

The coupling of **2b** with 6-chloro-purine gives rise to the coupling product **3e** in good yield. The elimination to the furyl nucleoside **4e** proved to be difficult. BCl_3 in acetonitrile gave the desired elimination product in 40% yield, which was the best we could attain so far.

An optimization of this reaction and attempts for the hydrogenation of **4e** are currently under investigation.

This new synthetic principle, combining "furan chemistry" with "nucleoside chemistry" (via hydrogenation), is highly promising because it opens new routes to known as well as new nucleoside analogues and avoids some difficulties encountered in the classical approaches. Antiviral activity and cytotoxic evaluations of selected compounds are in progress.

Acknowledgment. We thank Prof. J. Weber for his help in the conformational studies of compound **4b** by dynamic ^{1}H NMR. Prof. A. Fürstner, Max-Planck-Institut für Kohlenforschung, Germany, is thanked for helpful discussions.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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